

DETAILED ACTION

Information Disclosure Statement

The information disclosure statement (IDS) submitted on July 28, 2006 and May 30, 2007, have been considered by the Examiner. The submission is in compliance with the provisions of 37 CFR § 1.97. Enclosed with this Office Action is a return-copy of the Form PTO-1449 with the Examiner's initials and signature indicating those references that have been considered.

Status of the Application and Claims

This Application is a 371 of PCT/EP2005/001180, filed on April 2, 2005, which claims priority to US Provisional Application No. 60/541,984, filed on February 5, 2004.

Claims 1-3 and 5-12 are currently pending and are under consideration in this Office Action.

Claim Objection

Claim 1 is objected to because of inadvertent topographical error. The word inhibitor rather than inibitor should precede IAP in the claim. Correction is required.

Claim Rejections - 35 USC § 112—Written Description Requirement

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which

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it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3 and 6-12 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the claimed invention.

The claims are drawn to a pharmaceutical combination comprising (a) a DNA topoisomerase inhibitor compound and (b) an IAP inhibitor compound. The IAP inhibitor compound, as described in the specification, can include a plethora of pyrrolidine amide compounds. Thus, the claims are drawn to a myriad of a genus of pyrrolidine amide compounds that is defined only by biological activity.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of the complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present is that of the disclosure of chemical structures of two IAP inhibitors. There is no description of structural characteristics that are required to maintain biological activity. Accordingly, in the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus of the pyrrolidine amide compounds

Whether a few compounds known to act as inhibitor of the claimed enzyme are known in the art is not the issue; the claims are drawn to methods comprising administering any compound, including those known and those yet to be identified for inhibiting the growth of tumor cells in an organism. Applicant provides no guidance for identifying additional IAP inhibitor compounds except for trial-and-error screening: page 10, examples 1-3 and page 11, unlabeled data tables of the specification. The cited claims are drawn in part to a method for inhibiting the growth of tumor cells in an organisms comprising administering unspecified therapeutic agents to patients.

In University of Rochester v. G.D. Searle & Co., 68 USPQ2d 1424 (DC WNY 2003), at issue was a patent directed to method for inhibiting prostaglandin (PGHS-2) synthesis in a patient using an unspecified compound. The District Court of Western New York evaluated the level of disclosure required to satisfy the written description. In their decision (which was later affirmed by the CAFC), the District Court wrote, "The real issue here is simply whether a written description of a claimed method of treatment is adequate where a compound that is necessary to practice that method is described only in terms of its function, and where the only means provided for finding such a compound is essentially a trial-and-error process."

The patent in *Rochester* does no more than describe the desired function of the compound called for, and it contains no information by which a person of ordinary skill in the art would understand that the inventors possessed the claimed invention. At best, it simply indicates that one should run tests on a wide spectrum of compounds in the hope that at least one of them will work. The specification of the patent in *Rochester*

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states that the invention comprises, *inter alia*, "assays for screening compounds, including peptides, polynucleotides, and small organic molecules to identify those that inhibit the expression or activity of the PGHS-2 gene product; and methods of treating diseases characterized by aberrant PGHS-2 activity using such compounds." Nowhere, however, does it specify which "peptides, polynucleotides, and small organic molecules" have the desired characteristic of selectively inhibiting PGHS-2.

The *Rochester* court cited the CAFC in *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316 (63 USPQ2d 1609), which adopted the standard set forth in the Patent and Trademark Office ("PTO") Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, 1 "Written Description" Requirement ("Guidelines"), 66 Fed. Reg. 1099 (Jan. 5, 2001), which state that the written description requirement can be met by "showing that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics," including, *inter alia*, "functional characteristics *when coupled with a known or disclosed correlation between function and structure*" *Enzo*, 296 F.3d at 1324-25 (quoting Guidelines, 66 Fed. Reg. at 1106 (emphasis added)).

The *Rochester* court also cited the CAFC in *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1568 [43 USPQ2d 1398] (Fed. Cir. 1997), in which the court drew a distinction between genetic material and other chemicals; in drawing this distinction, however, the court also stated that "[i]n claims involving [non-genetic] chemical materials, *generic formulae usually indicate with specificity what the generic claims encompass*. One skilled in the art can distinguish such a formula from others and *can identify many of the species* that the claims encompass. Accordingly,

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such a formula is normally an adequate description of the claimed genus." 119 F.3d at 1568 (emphasis added). There is no such specificity here, nor could one skilled in the art identify any particular enzymatic effector encompassed by the claims.

The "written description" requirement may be satisfied by using such descriptive means as words, structures, figures, diagrams, formulas, etc., that fully set forth the claimed invention. See *Noelle v. Lederman*, 355 F.3d 1343, 1349, 69 USPQ2d 1508, 1514 (Fed. Cir. 2004) and *Lockwood v. American Airlines, Inc.*, 107 F.3d at 1572, 41 USPQ2d at 1966. A definition by function alone "does not suffice" to sufficiently describe a coding sequence "because it is only an indication of what the gene does, rather than what it is." *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d at 1568, 43 USPQ2d at 1406 (Fed. Cir. 1997) (discussing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir. 1991)). In *Fiefs v. Ravel*, 984 F.2d at 1169-71, 25 USPQ2d at 1605-06 (1993), the CAFC found that "a mere wish or plan for obtaining the claimed chemical invention" is not sufficient to describe a chemical invention (discussed in *Eli Lilly* at 1404).

The fact pattern in this case is similar to that in *Rochester*. In *Rochester*, there were no compounds known to have the required function, and in the instant application, only compounds C and D are disclosed. The key similarity between the cases, and the one relevant to this ground of rejection, is the fact that no method (other than trial-and-error) is provided for identifying compounds having the desired function. For this reason, the rejection due to lack of written description is proper

Therefore, only written description, but not the full breadth of the claims, meets the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes it clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see *Vas-Cath* at page 1115). See also *In re Barker*, 559 F.2d 588, 591, 194 USPQ 470, 472 (CCPA 1977) (a specification may be sufficient to enable one skilled in the art to make and use the invention, but still fail to comply with the written description requirement).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 10 and 12 are rejected under 35 U.S.C. 102(b) as being anticipated by *J. Biol. Chem.*, **2002**, 277(46), 44236-44243, To Arnt et al (hereinafter “Arnt”, cited by the Applicant and submitted by the Applicant in the Instant Application).

The instant invention is drawn to a combination therapy for the regulation of apoptosis or program cell death comprising IAP inhibitors which are compounds that are known to inhibit the binding of the Smac proteins to inhibitors of Apoptosis Proteins (IAPs), and DNA topoisomerase inhibitors.

Specifically, claim 1 recites:

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A combination which comprises (a) a DNA topoisomerase inhibitor and (b) an IAP inhibitor, wherein the active ingredients are present in each case in free form or in the form of a pharmaceutically acceptable salt or any hydrate thereof, and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

Arnt teaches a combination comprising Smac/DIABLO (also known as Smac or DABLO), a known IAP inhibitor and diverse anticancer agents exemplified by camptothecin (SN-38) and etoposide. As evidenced by the Applicants' disclosure on page 2, ¶ 2 and page 3, ¶ 2 of the instant specification, camptothecin is a topoisomerase I inhibitor and etoposide is a topoisomerase II inhibitor. Arnt further teaches that IAP inhibitors induces apoptosis and enhances the antiploriferative effects of topoisomerase inhibitors (see abstract).

Since Arnt teaches a combination comprising IAP inhibitor and topoisomerase inhibitor, Arnt anticipates claim 1 (see abstract).

Claim 2 depends from claim 1, and further requires at least one pharmaceutically acceptable carrier. Arnt teaches glycerol (see page 44237, left column, ¶ 8 and Applicants' disclosure of diluents as example of a carrier on page 6, ¶ 5).

Regarding claim 10, Arnt teaches combined preparation comprising (a) one or more concentration (unit dosage) of SN-38 and (b) one or more concentration (unit dosage) of Smac (see page 44241, figure 6).

Regarding claim 12, Arnt teaches combined preparation comprising (a) one or more concentration (unit dosage) of etoposide and (b) one or more concentration (unit dosage) of Smac (see page 44241, figure 6).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-3 and 5-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over *J. Biol. Chem.*, **2002**, 277(46), 44236-44243, To Arnt et al (hereinafter "Arnt", cited by the Applicants and submitted by the Applicants in the Instant Application), in view of WO2004/005248 which claims priority to US Provisional Application No. 60/393,150, filed on February 07, 2002, to Sharma et al (hereinafter "Sharma", cited by the Applicants in the Instant Application), as evidenced by US Pub. No. 2001/0038826 to Placke et al (hereinafter "Placke").

The limitations of claims 1, 2, 10 and 12 as well as the application of the art, is described above, and hereby incorporated into the instant rejection.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of

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the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Although Arnt teaches a combination comprising IAP inhibitor and topoisomerase inhibitor, Arnt does explicitly teach a method for the treatment of a proliferative disease in a patient as required by the instant claims 3, 6-9 and 11. Furthermore, Arnt did not explicitly teach compound C and compound D as IAP inhibitor, as required by claim 5.

Sharma teaches the use of IAP inhibitors to treat proliferative diseases such as tumors and compositions comprising IAP inhibitors. Furthermore, Sharma also teaches that the compounds of the invention can be administered alone or in combination with other anticancer therapeutics (see ¶ bridging pages 11-12). The compound C and compound D of the instant invention are taught by Sharma (see page 16, example 1 and page 18, example 15).

Placke teaches that other anticancer drugs with different mechanisms of action can be combined with topoisomerase inhibitors to increase the likelihood of destroying tumors that are comprised of cells with many different drug sensitivities (¶ 0182).

In view of Arnt, it would have been *prima facie* obvious as evidenced by Placke, to combine the IAP inhibitors of Sharma with known topoisomerase inhibitors and use this combination to treat cancer.

The instant situation is amenable to the type of analysis set forth in *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) wherein the court held that it is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose. The idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant claims, one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success that by administering topoisomerase inhibitors in combination with IAP inhibitors as taught by Arnt and evidenced in Placke in view of the teachings of Sharma, one would achieve a method of treating cancer. While *In re Kerkhoven* is limited to the mechanical arts, the holdings in this case are pertinent to the present claims because the idea of combining two known anticancer drugs to treat cancer flows logically from the individual drugs being taught to be useful in treating cancer. As such, one skilled in the art would reasonably expect the combination of drugs to also be effective in treating cancer. This is especially true in the present case where the prior art teaches that combinations of topoisomerase inhibitors with other anticancer agents having different mechanisms of action are effective to treat cancer.

Lastly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have been produced by their combination. *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Thus the claims fail to patentably distinguish over the state of the art as represented by the cited references. Therefore, the invention as a whole was *prima facie* obvious at the time it was made.

Double Patenting

Non-Statutory

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to

be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

US Patent Application 12/516062

Claims 1-3 and 5-12 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1- 7, 9-17 and 19 of copending US Application No. 12/516062. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claimed subject matter in the Instant Application is fully disclosed in the referenced US Application and would be covered by any patent granted on that referenced US Application. The referenced US Application and the Instant US Application are claiming a common subject matter. The doxorubicin in the claimed combination in claim 11 of US Application No. 12/516062 is a topoisomerase inhibitor (see Placke, column 6, table 1).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusions

No claim is allowable.

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If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicants should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported in *ipsis verbis*, clarification on the record may be helpful). Should the Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

Correspondence

Any inquiry concerning this communication or earlier communications from the examiner should be directed to IBRAHIM D. BORI whose telephone number is (571)270-7020. The examiner can normally be reached on Monday through Friday 8:00AM-5:00PM(EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY S. LUNDGREN can be reached on 571-272-5541. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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